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OCULAR PENETRATION AND INTRAOCULAR PRESSURE (IOP) LOWERING ACTIVITY OF THE ANGIOTENSIN II (AII) ANTAGONISTS LOSARTAN AND L-158,338.

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Purpose: To assess the penetration of losartan and L-158,338 into the rabbit eye after topical application and their effects on the IOP of ocular hypertensive cynomolgus monkeys.
Methods: Penetration was indirectly assessed in albino rabbits using an ex-vivo assay. Aliquots of aqueous humor were sampled one hour after the bilateral topical instillation of one drop (50 uL) of 2% solutions of losartan or L-158,338 (3H-imidazo[4,5-B]pyridine,7-methyl-2-propyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]) and their ability to block ^{125}I-[Sar,Ile]-AII (SARILE) binding tc binding sites in a membrane fraction of rabbit iris+ciliary body (ICB) was determined. IOP was measured out to six hours using a pneumatic tonometer in lightly sedated cynomolgus monkeys in which IOP had previously been experimentally elevated by photocoagulating the trabecular meshwork with an argon laser.
Results: Inhibition constants (Ki) for SARILE binding sites in ICB membranes were 80 nM and 2 nM for losartan and L-158,338, respectively. These results were in good agreement with values found at the AT1 receptor subtype. In contrast a value of 72,000 nM was found for the AT2 selective compound WL-19. Concentrations in the aqueous humor were 50 nM and 120 nM for losartan and L-158,338, respectively. These values were 0.6- and 60-fold their respective Ki values. The instillation of 1% solutions of losartan and L-158,338 did not elicit meaningful and consistent reductions in the IOP of ocular hypertensive monkeys. Increasing the dose of L-158,338 to 2% also failed to lower IOP.
Conclusions: AII receptors in the rabbit ICB are of the AT1 subtype. Both topically applied losartan and L-158,338 penetrate into the rabbit eye but neither agent displayed meaningful IOP lowering activity in ocular hypertensive monkeys.

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EFFECT OF CARTEOLOL ON THE CYTOSKELETON AND THE PHAGOCYTOSIS CAPACITY OF CULTURED TRABECULAR CELLS.

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Purpose : Various studies suggest that changes induced in the cytoskeleton of cells in the trabecular meshwork might lead to increased outflow facility. The cells of the trabecular meshwork serve as a filter for the aqueous humour. We studied the effect of carteolol on the shape and phagocytosis of trabecular cells *in vitro*.
Methods : Cell cultures derived from the trabecular meshwork of bovine eye were incubated at 37°C with increased concentrations of carteolol, timolol and ethacrynic acid for different times (10 min. to 24 hours). Identification of actinin and ß-tubulin were performed by immunofluorescence. The ability of cells to phagocytose latex microspheres was studied by electron microscopy.
Results : Cells incubated with carteolol at high concentrations (≥ 0,5 mM) and 0,001 mM ethacrynic acid, show a condensation of cytoskeletal structures, a cell retraction and an apparent attenuation of cell-to-cell contacts. These changes in cell shape were fully reversed 24 hours after exposure. These modifications are not observed with timolol incubation. The capacity of phagocytosis of carteolol and timolol-treated cells is not modified compared to the control cells.
Conclusion : A correlation between changes in tissue architecture and increased outflow facility is largely demonstrated for ethacrynic acid. In any event, results obtained from this *in vitro* study may not be extrapolated directly to *in vivo* situation. However, these results indicate an impact of long-term carteolol treatment on the trabecular meshwork, without cytotoxic effect.

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INTRAOCULAR CONCENTRATIONS OF MITOMYCIN C: ARE NEW DEVICES FOR APPLICATION BENEFICIAL?

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Purpose Intraocular toxic effects of Mitomycin C (MMC) are caused by inadvertend penetration of MMC through the sclera during scleral application. In most studies, a cellulose sponge is used for this procedure. We used different devices for application in order to determine, whether these alter intraocular concentrations.

Methods Six eyes each of pigmented rabbits were treated with MMC with a concentration of 0.5 mg/ml. The devices used were -a cellulose sponge, -a scleral shield, -a pre-soaked soft contact lens, -a soft contact lens with 0.1 ml of MMC applied during surgery, -a direct subconjunctival injection of MMC. Intraocular concentrations were measured by HPLC from samples taken 60 minutes after application of MMC.

Results The concentrations of MMC were highly variable within each group. Between the different groups, aqueous concentrations ranged from 24.5 to 74.8 ng/ml; vitreous concentrations from 3.7 to 13.2 ng/ml; conjunctiva concentrations from 25.6 to 519.5 ng/mg; and sclera concentrations from 9.1 to 41.0 ng/mg. There was no statistical difference between the concentrations in the tissues of the different groups.

Conclusion This study confirmed the intraocular penetration of high amounts of MMC. The use of different devices for delivery of MMC did not result in significantly different concentrations in ocular tissues except for subconjunctival injections with no irrigation. The high variability of measurements may explain the clinical phenomenon, that some eyes develop hypotony and others not.

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SUBLINGUAL TIMOLOL - an alternative to topical medication in glaucoma ?

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Objectives: To assess whether timolol drops lower intraocular pressure (IOP) when given sublingually. This route of administration would be useful for glaucoma patients who are unable to instil their own drops eg. because of stroke, poor vision, arthritis, poor coordination, blepharospasm.

Design: A placebo controlled, randomised, double masked, cross over study.

Method: 12 ocular hypertensive patients with intraocular pressures over 21mmHg, normal optic discs and full visual fields by Humphrey perimetry. Administration of single dose units of timolol maleate 0.5% drops and normal saline drops. Both are instilled in one eye or sublingually. The intraocular pressures of both eyes, pulse rate and blood pressure are all measured both before and after each type of drop and route of administration.

Results: 2 hours after instillation of timolol in one eye, the IOP in the treated eye was reduced by a mean of 8.5mmHg (P=0.0000), and by 1.66mmHg in the fellow eye (P=0.0287). 2 hours after sublingual instillation of timolol, the IOP was reduced by 7.55mmHg in the study eye (p=0.0000) and by 7.7mmHg in the fellow eye (p=0.0000).

Conclusions: Our results show that sublingual treatment is almost as effective as topical treatment in lowering a raised IOP. We recommend a trial of the sublingual route of timolol administration in patients who are unable to insert their own eyedrops.